(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 231 996 A2

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 87300064.0

(22) Date of filing: 06.01.87

(51) Int. Cl.[3]: C 07 D 401/06
C 07 D 403/06, C 07 D 405/06
C 07 D 409/06, A 61 K 31/445

(30) Priority: 07.01.86 DK 51/86
03.03.86 DK 956/86

(43) Date of publication of application:
12.08.87 Bulletin 87/33

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

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(54) **Novel amino acid derivatives.**

(57) Phenylbutene derivatives having optionally substituted phenyl and pyrrolyl, furanyl, pyridinyl, pyrazinyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrrolodinyl, tetrahydrofuranyl, piperidinyl, piperazinyl or alkylthienyl in the 4-position and 3-carboxypiperid-1-yl, 3-carboxytetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl in the 1-position potentiate GABA'ergic neurotransmission.

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SUMMARY OF THE INVENTION

The present invention relates to novel N-(butenyl-substituted) azaheterocyclic carboxylic acids of the general formula I

$$\begin{array}{l} R^1\text{-}\underset{\displaystyle R^2}{\underset{|}{C}}\text{=CH-}CH_2\text{-}CH_2\text{-}R^3 \end{array} \qquad (I)$$

wherein R^1 represents phenyl optionally substituted by one, two or more substituents selected from the group consisting of halogen, lower alkyl, and alkoxy, R^2 represents pyrrolyl, furanyl, pyridinyl, pyrazinyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl or (lower alkyl)thienyl each of which may be substituted by one, two or more substituents selected from the group consisting of halogen, lower alkyl, and alkoxy, and R^3 represents 3-carboxypiperid-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl or the corresponding amides or lower alkyl esters, or salts thereof. These compounds have interesting and valuable pharmacological properties.

BACKGROUND OF THE INVENTION

In the last decade, intensive pharmacological research concerning γ-aminobutyric acid (hereinafter designated GABA), a neurotransmitter in the central nervous system, has taken place.

Increased GABA'ergic activity is useful in the treatment of anxiety, pain, epilepsy and muscular and movement disorders. Furthermore, these compounds can be used as sedatives.

In U.S. patent specification No. 4,383,999 (Smithkline Beckmann Corporation) some derivatives of N-(4-phenyl-3-butenyl)azaheterocyclic carboxylic acids which have, furthermore, inter alia, phenyl, p-fluorophenyl, cyclohexyl or thienyl in the 4-position, are described.

According to J.Pharm.Exp.Therap. 228 (1984), 109 et seq., N-(4,4-diphenyl-3-butenyl)nipecotic acid (designated SK&F 89976A), N-(4,4-diphenyl-3-butenyl)guvacine (designated SK&F 100330A), N-(4,4-diphenyl-3-butenyl)-β-homoproline (designated SK&F 100561) and N-(4-phenyl-4-(2-thienyl)-3-butenyl)nipecotic acid (designated SK&F 100604J) are orally active inhibitors of GABA uptake.

DETAILED PRACTICE OF THIS INVENTION

It has now been found that novel compounds of the general formula I stated in Claim 1, below, exhibit GABA uptake inhibitory properties and possess useful pharmacological properties on the central nervous system, i.e., a selective enhancement of GABA activity. Surprisingly, these effects are superior to those of previously known compounds. Compounds of formula I may be used for treatment of, for example, pain, anxiety, epilepsy, certain muscular and movement disorders and other neurological disorders and as sedatives and hypnotics.

Herein pyrrolyl is 2-pyrrolyl or 3-pyrrolyl, furanyl is 2-furanyl or 3-furanyl, pyridinyl (pyridyl) is 2-pyridyl, 3-pyridyl or 4-pyridyl, pyrazinyl is 2-pyrazinyl or 3-pyrazinyl, imidazolyl is 2-imidazolyl, 4-imidazolyl or 5-imidazolyl, pyrazolyl is 3-pyrazolyl, 4-pyrazolyl or 5-pyrazolyl, pyrimidinyl is 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl or 6-pyrimidinyl, pyrrolidinyl is 2-pyrrolidinyl or 3-pyrrolidinyl, tetrahydrofuranyl is 2-tetrahydrofuranyl or 3-tetrahydrofuranyl, piperidinyl (piperidyl) is 2-piperidyl, 3-piperidyl or 4-piperidyl, piperazinyl is 2-piperazinyl, 3-piperazinyl or 4-piperazinyl and thienyl is 2-thienyl or 3-

thienyl. Furthermore, halogen is, preferably, chloro, bromo and fluoro. The lower alkyl group contains less than 8 carbon atoms, preferably less than 5 carbon atoms, and some preferred alkyl groups are methyl and ethyl. The lower alkoxy group contains less than 8 carbon atoms, preferably less than 5 carbon atoms, and some preferred alkoxy groups are methoxy and ethoxy. Preferably, (lower alkyl)thienyl is 3-methylthien-2-yl. Specific examples of substituted groups R^1 and R^2 are N-methylpyrrol-2-yl and N-methylpyrrol-3-yl.

Compounds of formula I are, for example:
N-(4-(N-methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(N-methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(N-methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(N-methylpyrrol-3-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(N-methylpyrrol-3-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(N-methylpyrrol-3-yl)-4-phenylbut-3-en-1-yl)-β-homoproline
N-(4-(furan-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(furan-2-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(furan-2-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(furan-3-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(furan-3-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(furan-3-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-phenyl-4-(pyridin-2-yl)but-3-en-1-yl)nipecotic acid,
N-(4-phenyl-4-(pyridin-2-yl)but-3-en-1-yl)guvacine,
N-(4-phenyl-4-(pyridin-2-yl)but-3-en-1-yl)-β-homoproline,
N-(4-phenyl-4-(pyridin-3-yl)but-3-en-1-yl)nipecotic acid,
N-(4-phenyl-4-(pyridin-3-yl)but-3-en-1-yl)guvacine,
N-(4-phenyl-4-(pyridin-3-yl)but-3-en-1-yl)-β-homoproline,
N-(4-phenyl-4-(pyridin-4-yl)but-3-en-1-yl)nipecotic acid,
N-(4-phenyl-4-(pyridin-4-yl)but-3-en-1-yl)guvacine,
N-(4-phenyl-4-(pyridin-4-yl)but-3-en-1-yl)-β-homoproline,
N-(4-phenyl-4-(pyrazin-2-yl)but-3-en-1-yl)nipecotic acid,

N-(4-phenyl-4-(pyrazin-2-yl)but-3-en-1-yl)guvacine,
N-(4-phenyl-4-(pyrazin-2-yl)but-3-en-1-yl)-β-homoproline,
N-(4-phenyl-4-(pyrazin-3-yl)but-3-en-1-yl)nipecotic acid,
N-(4-phenyl-4-(pyrazin-3-yl)but-3-en-1-yl)guvacine,
N-(4-phenyl-4-(pyrazin-3-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(1-methylimidazol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(1-methylimidazol-2-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(1-methylimidazol-2-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(1-methylimidazol-4-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(1-methylimidazol-4-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(1-methylimidazol-4-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(1-methylimidazol-5-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(1-methylimidazol-5-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(1-methylimidazol-5-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(N-methylpyrrol-2-yl)but-3-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(N-methylpyrrol-2-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(N-methylpyrrol-2-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(N-methylpyrrol-2-yl)but-3-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(N-methylpyrrol-3-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(N-methylpyrrol-3-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(pyridin-3-yl)but-2-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(pyridin-3-yl)but-2-en-1-yl)guvacine,

N-(4-(2-methylphenyl)-4-(pyridin-3-yl)but-2-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(pyridin-3-yl)but-3-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(pyridin-3-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(pyridin-3-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(N-methylpyrazol-3-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(N-methylpyrazol-3-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(N-methylpyrazol-3-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(N-methylpyrazol-4-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(N-methylpyrazol-4-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-N-methylpyrazol-4-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(N-methylpyrazol-5-yl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(N-methylpyrazol-5-yl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(N-methylpyrazol-5-yl)-4-phenylbut-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-3-yl)but-3-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-3-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-3-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-4-yl)but-3-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-4-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-4-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-5-yl)but-3-en-1-yl)nipecotic acid,

N-(4-(2-methylphenyl)-4-(N-methylpyrazol-5-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(N-methylpyrazol-5-yl)but-3-en-1-yl)-β-homoproline,
N-(4-(2-methylphenyl)-4-(1-methylimidazol-2-yl)but-3-en-1-yl)nipecotic acid,
N-(4-(2-methylphenyl)-4-(1-methylimidazol-2-yl)but-3-en-1-yl)guvacine,
N-(4-(2-methylphenyl)-4-(1-methylimidazol-2-yl)but-3-en-1-yl)-β-homoproline
N-(4-(3-methyl-2-thienyl)-4-phenylbut-3-en-1-yl)nipecotic acid,
N-(4-(3-methyl-2-thienyl)-4-phenylbut-3-en-1-yl)guvacine,
N-(4-(3-methyl-2-thienyl)-4-phenylbut-3-en-1-yl)homoproline
and salts thereof.

Compounds of formula I may exist as geometric and optical isomers and all isomers and mixtures thereof are included herein. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallisation.

One embodiment of this invention is non-toxic pharmaceutically acceptable salts of compounds of formula I. Salts include those derived from inorganic or organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, lactic, maleic and phthalic acid.

Compounds of formula I may be prepared by N-alkylation of a compound of the general formula II

$$H\text{-}R'^{3} \qquad \text{(II)}$$

wherein R'^{3} has the same meaning as R^{3} with the proviso that the carboxy group is protected, for example, by an ester group, with a compound of the general formula III

$$\begin{array}{l} R^1\text{-}C\text{=}CH\text{-}CH_2\text{-}CH_2X \\ \quad\ | \\ \quad R^2 \end{array} \qquad \text{(III)}$$

wherein R^1 and R^2 are as defined in Claim 1, and X represents halogen. This reaction may be carried out in an inert solvent in the presence of an alkali metal carbonate, for example, potassium carbonate at, for example, room temperature, for from about 1 to 12 days. The solvent may conveniently be acetone or N,N-dimethylformamide. Compounds of formula I may be prepared by hydrolysis of the resulting ester, preferably at room temperature in a mixture of an aqueous sodium hydroxide solution and an alcohol such as methanol or ethanol for from about 0.5 to 4 hours.

Compounds of formula III may be prepared by reacting the appropriate disubstituted ketones with a Grignard reagent, i.e., cyclopropyl magnesium bromide, followed by ring opening of the intermediate cyclopropyl carbinol derivative by treatment with hydrogen bromide in acetic acid. Alternative conditions involve the use of trimethylsilyl chloride and lithium iodide in, for example, dichloromethane.

Compounds of formula I are useful because they possess pharmacological activity in man. In particular, the compounds of formula I are useful as inhibitors of GABA uptake.

For the above indications, the dosage will vary depending on the compound of formula I employed, on the mode of administration and on the therapy desired. However, in general, satisfactory results are obtained with a dosage of from about 15 mg to about 2 g of compounds of formula I, conveniently given from 1 to 5 times daily, optionally in sustained release form. Usually, dosage forms suitable for oral administration comprise from about 25 mg to about 1 g of the compounds of formula I admixed with a pharmaceutical carrier or diluent. No toxic effects have been observed at these levels.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit approximately the same order of activity as the free base forms.

This invention also relates to pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutical carrier or diluent. The compositions of this invention may be prepared by conventional techniques to appear in conventional forms, for example, capsules or tablets.

The pharmaceutical carrier employed may be conventional solid or liquid carriers. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water. Similarly, the carrier or diluent may include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier for oral administration is used, the preparation can be tabletted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but, usually, will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may appear in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension.

The pharmaceutical compositions of this invention can be made following the conventional techniques of the pharmaceutical industry involving mixing, granulating and compressing or variously mixing and dissolving the ingredients as appropriate to give the desired end product.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired place, such as orally or parenterally, the oral route being preferred.

The features disclosed in the foregoing description and in the following examples and claims may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which, however are not to be construed as limiting. The examples illustrate some preferred embodiments.

Hereinafter T.l.c. is thin layer chromatography, THF is tetrahydrofuran and EtOH is ethanol.

Example 1

Cyclopropyl-(N-methylpyrrol-2-yl)phenylmethanol

To a suspension of magnesium turnings (5.29 g, 0.22 mole) in anhydrous tetrahydrofuran (70 ml), cyclopropyl bromide (26.35 g, 0.22 mole) in tetrahydrofuran (50 ml) was added dropwise under nitrogen. The reaction mixture was heated at reflux for one hour after the initial exotherm had subsided before N-methylpyrrol-2-ylphenylketone (13.3 g, 0.072 mole) (J.White and G. McGillivray, J.Org.Chem., (1977), 42, 4248, R. Greenhouse and C. Ramirez, J.Org.Chem., (1985), 50, 2961) in anhydrous tetrahydrofuran (50 ml) was introduced dropwise. After heating the reaction mixture at reflux for 3 hours it was cooled and saturated, aqueous ammonium chloride solution (95 ml) and water (150 ml) were added. The mixture was extracted with ethyl acetate (3 x 200 ml) and the combined extracts were dried ($MgSO_4$). Flash chromatography of the residue on evaporation on silica gel eluting with heptane/tetrahydrofuran (9:1) provided the title compound as an oil (9.9 g, 46%) which solidified on standing. T.l.c. rf = 0.35 (SiO_2, heptane/THF (7:3)).

Ring opening of cyclopropylcarbinol: Method A
1-Bromo-4-(N-methylpyrrol-2-yl)-4-phenylbut-3-ene

Cyclopropyl-(N-methylpyrrol-2-yl)phenylmethanol was dissolved in acetic acid (60 ml) and a mixture of acetic acid (30 ml) and 48% hydrobromic acid (15 ml) was added at 5°C. The mixture was stirred for 30 minutes and poured into water (300 ml). The resultant emulsion was extracted with ethyl acetate (2 x 100 ml). The combined organic layers were washed with saturated sodium bicarbonate solution and brine and dried (Na_2SO_4). The concentrate, containing some acetic acid, was passed through a silica column (Merck Art 9385) with heptane/tetrahydrofuran (19:1) as eluent. After further flash chromatography in the same solvent system, the pure bromide (Z isomer) was obtained. T.l.c. rf = 0.35 (SiO_2, heptane/THF (9:1)).

Method B (G. Balme, G. Fournet and J. Gore, Tetrahedron. Lett., (1905), 1907
4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl chloride and iodide

Cyclopropyl-(N-methylpyrrol-2-yl)phenylmethanol (6.46 g, 28.4 mmol) was dissolved in dichloromethane (200 ml) and lithium iodide (4.56 g, 31.4 mmol) was introduced. The mixture was cooled to 0°C, and chlorotrimethylsilane (3.6 ml, 28.4 mmol) was added dropwise. After 2 hours at 0°C, the reaction mixture was filtered and evaporated to a dark green oil (7.28 g). Flash chromatography on silica gel (Merck Art 9385) eluting with heptane/tetrahydrofuran (19:1) provided the title compounds as an oil (6.3 g, 64%) (a mixture of E and Z isomers). T.l.c. rf = 0.29 (SiO_2, heptane/THF (9:1)).

R-N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester

4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl chloride and iodide (3.0 g, 8.7 mmol) were dissolved in anhydrous acetone (50 ml) and dried potassium carbonate (4.8 g, 34.8 mmol), sodium iodide (1.3 g, 8.7 mmol) and the R-enantiomer of ethyl nipecotate (1.462 g, 9.3 mmol) (A.M. Akkerman et al., Rec.Trav.Chem., 1951, 70, 899; G. Bettoni et al., Gazz.Chem.Ital., 1972, 102, 189) was added. The suspension was stirred at room temperature for 10 days, filtered and evaporated to a gummy residue which was purified by flash chromatography on silica gel (Merck Art 9385). Elution with heptane/tetrahydrofuran (19:1) provided the title ester (1.74 g, 54%) as an oil, T.l.c. rf = 0.06 (SiO_2, heptane/THF (9:1)).

R-N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid hydrochloride (NO-05-0356)

R-N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester (1.74 g, 4.7 mmol) was dissolved in ethanol (50 ml) and 10 N sodium hydroxide solution (8.9 ml) was added. The solution was stirred at room temperature for 30 minutes and cooled to 0°C. The pH was adjusted to 5 with 4 N hydrochloric acid solution, and the solution was extracted with dichloromethane (4 x 25 ml). The combined extracts were washed with water (10 ml) and dried ($MgSO_4$). The residue on evaporation was treated with water (100 ml) and activated charcoal. Filtration through a millipore filter gave a solution which was freeze-dried to give the product as a cream solid (1.53 g, 82%). It was found that the E and Z isomers could be separated by HPLC.

Example 2

N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester

1-Bromo-4-(*N*-methylpyrrol-2-yl)-4-phenylbut-3-ene (4.58 g, 15.9 mmol) was dissolved in anhydrous acetone (115 ml) and dried potassium carbonate (8.78 g, 63.6 mmol) was introduced, followed by ethyl nipecotate (3.25 g, 20.7 mmol). The reaction mixture was stirred at room temperature for 12 days, filtered and evaporated to give a brown oil (6.4 g). Column chromatography on silica gel (Merck Art 15111) eluting with heptane/tetrahydrofuran (19:1) provided the title compound as an oil (3.68 g, 63%). T.l.c. rf = 0.31 (SiO_2, THF/heptane (3:7)).

N-(4-N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid hydrochloride (NO-05-0165)

N-(4-(*N*-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester (2.75 g, 7.5 mmol) was dissolved in ethanol (70 ml). 10 N sodium hydroxide solution (14 ml) was introduced, and the solution was stirred for 30 minutes at room temperature before being cooled to 0°C. The pH was adjusted to 7 with 4 N hydrochloric acid solution, and the reaction mixture was extracted with dichloromethane (4 x 100 ml) (emulsion). The combined organic extracts were washed with a mixture of saturated brine (20 ml) and water (20 ml). The layers were separated, and the aqueous phase was washed with dichloromethane (100 ml). The combined extracts were dried (Na_2SO_4) and filtred through "hyflo". The filtrate was evaporated and the residue dissolved in 150 ml water, decolourised (charcoal) and freeze dried. The title amino acid was obtained as a dense white powder (Z isomer) (1.83 g, 72%). T.l.c. rf = 0.33 (SiO_2, dichloromethane/methanol (4:1)).

Example 3

2-Benzoyl-N-ethylpyrrole

2-Benzoylpyrrole (ref. as in Example 1) (10.27 g, 0.06 mole) was dissolved in dry N,N-dimethylformamide (120 ml) and combined with sodium hydride (2.016 g, 0.084 mole) (60% oil dispersion) in dry N,N-dimethylformamide (120 ml). The reaction mixture was stirred at room temperature for 18 hours and water (100 ml) was added. The reaction mixture was extracted with diethyl ether (3 x 100 ml) and the combined extracts were washed with water (200 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound as an oil (11.74 g, 98%). T.l.c. rf = 0.53 (SiO_2, dichloromethane/methanol (98:2)).

This ketone was converted into a mixture of 4-(N-ethylpyrrol-2-yl)-4-phenylbut-3-en-1-yl chloride and iodide by the method described in Example 1 (using Method B)

R-N-((4-N-Ethylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester

4-(N-Ethylpyrrol-2-yl)-4-phenylbut-3-en-1-yl chloride and iodide (3.16 g, 9 mmol) were dissolved in anhydrous acetone (50 ml) and dried potassium carbonate (4.97 g, 36 mmol), sodium iodide (2.7 g, 18 mmol) and the R-enantiomer of ethyl nipecotate (1.93 g, 13.7 mmol) were introduced. The suspension was stirred at room temperature for 10 days, filtered and evaporated to a residue. The residue was purified by column chromatography on silica gel (Merck Art 9385) eluting with heptane/tetrahydrofuran (19:1), providing the title ester (1.50 g, 43%) as a gum. T.l.c. rf = 0.21 (SiO_2, heptane/THF (4:1)).

R-N-((4-N-Ethylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid

R-N-((4-N-Ethylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester (0.14 g, 0.4 mmol) was hydrolysed by the method outlined in Example 1. The title acid was obtained as a freeze-dried solid (Z isomer) (54 mg, 33%); m.p. 56.5 - 60°C (decomposition).

Example 4

N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine methyl ester

4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl chloride and iodide (1.46 g, 4.3 mmol) (Example 1) were dissolved in anhydrous acetone (30 ml) and dried potassium carbonate (2.37 g, 17.2 mmol), sodium iodide (0.645 g, 4.3 mmol) and guvacine methyl ester hydrochloride. (0.995 g, 5.6 mmol) were added. The suspension was stirred at room temperature for 5 days, and worked up as described in Example 1 to give the title ester (1.1 g, 72%) as a fawn oil (mixture of E and Z isomers). T.l.c. rf = 0.05 (SiO_2, heptane/THF (9:1)).

N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine hydrochloride (mixture of E and Z isomers) (NO-05-0387)

N-(4-(N-(Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine (1.02 g, 2.9 mmol) was hydrolysed by the method outlined in Example 1. The title acid was obtained as a freeze dried solid (0.64 g, 52%); melting point: 81.5 - 84°C (E and Z isomers).

N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine methyl ester

1-Bromo-4-(N-methylpyrrol-2-yl)-4-phenylbut-3-ene (0.60 g, 2.08 mmol) was dissolved in anhydrous acetone (20 ml) and dried potassium carbonate (1.10 g, 8 mmol) was introduced, followed by guvacine methyl ester hydrochloride (0.37 g, 2.08 mmol). The reaction mixture was stirred at room temperature for 10 days and worked up as described in Example 1 to give the title ester (Z isomer) (380 mg, 52%) as an oil. T.l.c. rf = 0.32 (SiO_2, heptane/THF (9:1))

N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine hydrochloride (Z-isomer) NO-05-0227

N-(4-(N-Methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)guvacine methyl ester was hydrolysed by the method outlined in Example 1. The title acid was obtained as a freeze dried white powder (60 mg, 38%); melting point: 70°C.

Example 5

Cyclopropylphenyl-(4-pyridyl)methanol

Magnesium turnings (2.65 g, 0.109 mole) in dry tetrahydrofuran (50 ml) was treated dropwise with cyclopropyl bromide (13.2 ml, 0.109 mole). The reaction mixture was heated at reflux for 1 hour after the initial exotherm had subsided, and then 4-benzoylpyridine (10 g, 0.0545 mole) was introduced. Heating at reflux was continued for 2 hours, the reaction mixture was cooled and saturated ammonium chloride solution (70 ml) was added. This aqueous phase was extracted with ethyl acetate (3 x 200 ml) and the combined extracts were dried ($MgSO_4$). Evaporation gave a crude solid residue (6.23 g) which

was recrystallized from toluene to give the title alcohol (2.57 g, 21%), m.p. 171 - 172°C. T.l.c. rf = 0.065 (SiO_2, THF/heptane (3:7)).

<u>1-Bromo-4-phenyl-4-(4-pyridyl)but-3-ene</u>

Cyclopropylphenyl-4-(4-pyridyl)methanol (2.4 g, 10.6 mmol) was dissolved in acetic acid (25 ml). The solution was cooled to 0°C. A 47% solution of hydrogen bromide (5 ml) was added and the reaction mixture was stirred at room temperature for 3.5 hours, and at 40°C for 1 hour. The reaction mixture was poured into water (100 ml) and this aqueous phase was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution (40 ml) and saturated brine (40 ml) and dried ($MgSO_4$). Evaporation gave a crude product (3.26 g) which was purified by flash chromatography on silica gel (Merck Art 9385). Elution with heptane/ethyl acetate (7:3) provided an oil (1.38 g, 45%) which solidified on standing. T.l.c. rf = 0.13 (SiO_2, heptane/ethyl acetate (7:3)).

<u>N-(4-Phenyl-4-(4-pyridyl)but-3-en-1-yl)nipecotic acid, ethyl ester</u>

1-Bromo-4-phenyl-4-(4-pyridyl)but-3-ene (1.0 g, 3.5 mmol), ethyl nipecotate (0.72 g, 4.6 mmol) and potassium carbonate (1.93 g, 14.0 mmol) were stirred at room temperature for 5 days. The reaction mixture was filtered, and evaporated to a residue which was purified by flash chromatography on silica gel (Merck Art 9385). Elution with dichloromethane/ethanol/25% ammonium solution (190:9:1) provided the title compound as an oil. T.l.c. rf = 0.23 (SiO_2, $CH_2Cl_2/EtOH/NH_3$ (190:9:1)).

N-(4-Phenyl-4-(4-pyridyl)but-3-en-1-yl)nipecotic acid hydrochloride (NO-05-0358

N-(4-Phenyl-4-(4-pyridyl)but-3-en-1-yl)nipecotic acid ethyl ester was hydrolysed by the method outlined in Example 1. The title acid was obtained as a freeze dried solid.

Example 6

2-Methylphenyl-4-pyridylmethanol

Magnesium turnings (3.2 g, 0.131 mole) in dry tetrahydrofuran (50 ml) were treated dropwise with 2-bromotoluene (15 g, 0.087 mole). The reaction mixture was heated at reflux for 1 hour after the initial reflux had subsided. After cooling, 4-pyridylcarboxaldehyde (14.38 g, 0.131 mole) in dry tetrahydrofuran (30 ml) was introduced slowly, and subsequently the reaction mixture was heated at reflux for 2 hours. The reaction was worked up as in Example 5 (Grignard reaction) to give the title alcohol (5.92 g, 34%). T.l.c. rf = 0.24 (SiO_2, ethyl acetate).

4-(2-Methylbenzoyl)pyridine

Pyridinium chlorochromate (9.29 g, 43.1 mmol) was dissolved in dichloromethane (50 ml) and a solution of 2-methylphenyl-4-pyridylmethanol (5.72 g, 28.7 mmol) in dichloromethane (30 ml) was added. The reaction mixture became dark immediately, and was stirred for 2 hours at room temperature. Diethyl ether (350 ml) was added, and the reaction mixture was filtered through "hyflo" and evaporated to a dark oil (11.26 g). Flash chromatography on silica gel (Merck Art

9385) eluting with heptane/tetrahydrofuran (4:1) provided the title compound (2.74 g, 48%) as an oil. T.l.c. rf = 0.45 (SiO_2, ethyl acetate).

This ketone was converted into 1-bromo-4-(2-methylphenyl)-4-(4-pyridyl)but-3-ene by the method described in Example 1 (Method A).

N-(4-(2-Methylphenyl)-4-(4-pyridyl)but-3-en-1-yl)nipecotic acid ethyl ester

1-Bromo-4-(2-methylphenyl)-4-(4-pyridyl)but-3-ene (1.9 g, 7.6 mmol) was dissolved in anhydrous acetone (30 ml) and dried potassium carbonate (4.2 g, 30.4 mmol) and ethyl nipecotate (2.39 g, 15.2 mmol) were introduced. The suspension was stirred at room temperature for 18 hours, filtered and evaporated to a residue. The residue was purified by "flash" chromatography on silica gel (Merck Art 9385) eluting with heptane/tetrahydrofuran (7:3) to provide the title ester (0.67 g, 41%) as a reddish oil (a mixture of E and Z isomers). T.l.c. rf = 0.08 (SiO_2; heptane/THF (7:3)).

N-(4-(2-Methylphenyl)-4-(4-pyridyl)but-3-en-1-yl)nipecotic acid

N-(4-(2-Methylphenyl)-4-(4-pyridyl)but-3-en-1-yl)nipecotic acid ethyl ester (0.67 g, 1.8 mmol) was dissolved in ethanol (20 ml) and 10 N sodium hydroxide solution (3.42 ml) was added. The solution was stirred at room temperature for 0.5 hours, and the pH was adjusted to 5 with 4 N hydrochloric acid. The solution was applied to a column of Dowex 50WX8 ion exchange resin (H^+ form). Elution with water followed by dilute ammonia solution provided the title acid (180 mg, 30%).

Example 7

2-Methylphenyl-(3-methyl-2-thienyl)methanol

The title compound was prepared from 2-bromotoluene (35.55 g, 0.208 mole), magnesium turnings (5.1 g, 0.208 mole) and 3-methylthiophene-2-aldehyde (23.6 g, 0.187 mole) by the method described in Example 6, using diethyl ether (150 ml) as solvent. The yield was 36.0 g (88%). T.l.c. rf = 0.39 (SiO_2, heptane/THF (7:3)).

3-Methyl-2-(2-methylbenzoyl)thiophene

2-Methylphenyl-(3-methyl-2-thienyl)methanol (36.0 g, 0.165 mole) was dissolved in dichloromethane (400 ml) and manganese dioxide (58 g, 0.667 mole) was added. The reaction mixture was heated at reflux for 18 hours, cooled and further manganese dioxide (30 g, 0.34 mole) was introduced; reflux was continued for a further 18 hours. The mixture was filtred and evaporated to a residue (32 g) which was distilled in vacuo (0.2 mm Hg). Fractions boiling at 100 - 120°C (4.8 g) and 120 - 132°C (21.0 g) were collected, giving the title compound as an oil (25.8 g, 72%).

The ketone was converted into 1-bromo-4-(2-methylphenyl)-4-(3-methyl-2-thienyl)but-3-ene by the method described in Example 1 (Method A)

R-N-(4-(2-Methylphenyl)-4-(3-methyl-2-thienyl)but-3-en-1-yl)nipecotic acid ethyl ester

1-Bromo-4-(2-methylphenyl)-4-(3-methyl-2-thienyl)but-3-ene (3.0 g, 9.34 mmol) was dissolved in anhydrous acetone (40 ml) and dried potassium carbonate (1.38 g, 10 mmol) potassium iodide (0.2 g, 1 mmol) and the R-enantiomer of ethyl

nipecotate (1.57 g, 10 mmol) were introduced. The suspension was stirred at room temperature for 18 hours, filtered, and evaporated to a residue. The residue was purified by "flash" chromatography on silica gel (Merck Art 9385) eluting with heptane/tetrahydrofuran (4:1), to provide the title ester (2.4 g, 65%) as an oil. T.l.c. rf = 0.40 (SiO_2, heptane/THF (7:3)).

R-N-(4-(2-Methylphenyl)-4-(3-methyl-2-thienyl)but-3-en-1-yl)nipecotic acid (NO-05-0340)

R-N-(4-(Z-Methylphenyl)-4-(3-methyl-2-thienyl)but-3-en-1-yl)nipecotic acid ethyl ester (1.4 g, 3.52 mmol) was hydrolysed by the method outlined in Example 1. The title acid was obtained as a solid (1.1 g, 85%); melting point: 65 - 67°C.

Example 8

Cyclopropyl-2-furylphenylmethanol

To a suspension of magnesium turnings (0.26 g, 10.5 mmol) in anhydrous tetrahydrofuran (6 ml) cyclopropyl bromide (1.28 g, 10.5 mmol) in tetrahydrofuran (5 ml) was added dropwise under nitrogen. The reaction mixture was heated at reflux for 1 hour after the initial exotherm had subsided before 2-benzoylfuran (12 g, 7.0 mmol) was added as a solution in tetrahydrofuran (10 ml). The reaction mixture was worked up as described in Example 1 to give the title alcohol as an oil. T.l.c. rf = 0.23 (SiO_2, heptane/THF (7:3)).

This compound was converted directly into 1-bromo-4-(2-furanyl)-4-phenylbut-3-ene by the method described in Example 1 (Method A).

N-(4-(2-Furanyl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester

1-Bromo-4-(2-furanyl)-4-phenylbut-3-ene (0.23 g, 0.83 mmol) was dissolved in anhydrous acetone (10 ml) and dried potassium carbonate (0.46 g, 3.32 mmol) was added, followed by ethyl nipecotate (0.16 g, 1 mmol). The suspension was stirred at room temperature for 9 days, filtered and evaporated to a residue. The residue was purified by column chromatography on silica gel (Merch Art 9385), eluting with heptane/tetrahydrofuran (7:3), to provide the title ester (140 mg, 47%) as an oil. T.l.c. rf = 0.36 (SiO_2, heptane/THF (7:3)).

N-(4-(2-Furanyl)-4-phenylbut-3-ene-1-yl)nipecotic acid

N-(4-(2-Furanyl)-4-phenylbut-3-en-1-yl)nipecotic acid ethyl ester (130 mg, 0.36 mmol) was hydrolysed by the method described in Example 1. The title acid was obtained as a freeze dried solid. T.l.c. rf = 0.43 (SiO_2, methanol).

Example 9

Preparation of Capsules.

Ingredients	Mg per Capsule
N-(4-(N-methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid	125
Magnesium stearate	2
Lactose	200

The above ingredients are thoroughly mixed and placed into hard gelatin capsules. Such capsules are administered orally to subjects in need of treatment from 1 - 5 times daily to enhance GABA'ergic activity in the central nervous system.

Example 10

Preparation of Tablets.

Ingredients	Mg per Tablet
N-(4-(N-methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid	200
Corn starch	46
Polyvinyl pyrrolidone	12
Magnesium stearate	1

The compound is thoroughly mixed with two thirds of the corn starch and granulated. The granules obtained are dried, mixed with the remaining ingredients and compressed into tablets.

The capsules or tablets thus prepared are administered orally. Similarly, other compounds of formula I can be used.

PHARMACOLOGICAL TEST

Introduction

The convulsions induced by loud noise in the DBA/2 strain of mice is regarded as a reliable model for evaluating antiepileptic drug effects, cf. E.N. Petersen et al.: Psychopharmacol. 83 (1984), 240, and A.G. Chapman et al.: Arzmeim.-Forsch. 10 (1984), 1261. The Rotarod and Traction tests were used to evaluate the sedative properties of the test drugs.

Methods

Male DBA/2 mice (8 ± 1 g) were used in all experiments. The animals were pretrained on the Rotarod (6 rpm; rod diameter 2.5 cm) for 1 minute. The compounds tested were injected intraperitoneally. Twenty-five minutes later, the

animals underwent a 2 minutes' test on the Rotarod. The number of failures to stay on the rod was counted. An error rate higher than 10 was assigned the maximum score of 10. Immediately after the Rotarod test, the animals were tested in a Traction test, cf. Psychopharmacol. above. In this test, the animal was required to maintain grasp on a thin rod (diameter 2.5 mm) with the forepaws for five seconds and, within this period of time, to show a traction response (grasping onto the rod with one of the hindlegs). The performance on the test was based on the absence or presence of the traction response with the 5 seconds' test period. Finally, after the Traction test, the animals were individually placed in a chamber in which they were exposed for 30 seconds to a 14 kHz sinus tone at 111 dB. During this period of time, the following behaviors were noted: "Wild running", clonic convulsions and death.

Drugs

The compounds tested were dissolved in distilled water or suspended in 5% chremophore. The injection volume was 0.2 ml/mouse.

Results obtained

In table I, below, the ratio ED_{50} Rotarod/ED_{50} tonic convulsions is given for the compounds tested. NO-05-0340 is R-N-(4-(2-methylphenyl)-4-(3-methyl-2-thienyl)but-3-en-1-yl)nipecotic acid and NO-05-0356 is R-N-(4-(N-methylpyrrol-2-yl)-4-phenylbut-3-en-1-yl)nipecotic acid.

Table I

Compound	Ratio
NO-05-0340	8
NO-05-0356	21
SK&F 100330A	1
SK&F 89976A	5
SK&F 100561	7

The features disclosed in the foregoing description and in the following claims may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

CLAIMS

1. Phenylbuten derivatives of the general formula I

$$\begin{array}{l} R^1\text{-}C\text{=}CH\text{-}CH_2\text{-}CH_2\text{-}R^3 \\ \quad\ | \\ \quad R^2 \end{array} \qquad (I)$$

wherein R^1 represents phenyl optionally substituted by one, two or more substituents selected from the group consisting of halogen, lower alkyl, and lower alkoxy, R^2 represents pyrrolyl, furanyl, pyridinyl, pyrazinyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl or (lower alkyl)thienyl each of which may be substituted by one, two or more substituents selected from the group consisting of halogen, lower alkyl, and lower alkoxy, and R^3 represents 3-carboxypiperid-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or salts thereof.

2. Derivatives, according to Claim 1, characterized in that R^3 is 3-carboxypiperid-1-yl or 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl.

3. Derivatives, according to Claim 1 or 2, characterized in that R^2 represents pyrrolyl, furanyl, pyridinyl, pyrazinyl, imidazolyl, pyrazolyl, pyrimidinyl, tetrahydrofuranyl, piperidinyl or (lower alkyl)thienyl each of which may be substituted by one, two or more substituents selected from the group consisting of halogen, lower alkyl, and alkoxy.

4. Derivatives, according to any one of the preceding claims, wherein R^2 is 2-pyrrolyl.

5. Derivatives, according to any one of the Claims 1 through 3, wherein R^2 is 2-furanyl.

6. Derivatives, according to any one of the Claims 1 through 3, wherein R^2 is 2-imidazolyl.

7. Derivatives, according to any one of the Claims 1 through 3, wherein R^2 is N-methylpyrazolyl.

8. Derivatives, according to any one of the Claims 1 through 3, wherein R^2 is 5-pyrimidinyl.

9. Derivatives, according to any one of the Claims 1 through 3, wherein R^2 is methylthienyl, preferably 3-methylthienyl, more preferred 3-methylthien-2-yl.

10. Derivatives, according to any one of the Claims 1 through 3, characterized in that R^1 is phenyl substituted by chloro, bromo, fluoro, methyl, ethyl or methoxy.

11. Derivatives, according to any one of the Claims 1 through 3, characterized in that the heterocyclic group is substituted with lower alkyl, preferably with methyl, ethyl, isopropyl or propyl.

12. Derivatives, according to any one of the Claims 1 through 3, wherein R^2 is N-methylpyrrol-2-yl.

13. Pharmaceutical compositions containing a compound of formula I stated in any one of the preceding claims or a salt thereof.

14. Compositions, according to Claim 13, characterized in that they contain from about 25 mg to about 1 g of the compound.

15. The use of compounds of formula I stated in Claim 1 or a salt thereof for the manufacture of a medicament, for example for increasing the GABA'ergic activity and/or for use as a sedative.

16. A process for preparing compounds of formula I stated in Claim 1 or a salt thereof, characterized in hydrolysing a compound of the general formula IV

$$\begin{array}{l} R^{1}-\underset{\displaystyle R^{2}}{\underset{|}{C}}=CH-CH_{2}-CH_{2}R'^{3} \end{array} \qquad (IV)$$

wherein R^1, R^2 and R'^3 each are as defined above, and, if desired, converting a compound of formula I into a salt thereof or converting a salt into a compound of formula I.